



⑩ Europäisches Patentamt  
European Patent Office  
Office européen des brevets

⑪ Publication number:

0 094 771  
B1

⑫

## EUROPEAN PATENT SPECIFICATION

⑯ Date of publication of patent specification: 05.08.87

⑮ Int. Cl.<sup>4</sup>: A 61 K 7/48, A 61 K 9/10,  
A 61 K 31/07

⑯ Application number: 83302554.7

⑯ Date of filing: 06.05.83

### ④ Skin treatment compositions.

⑥ Priority: 15.05.82 GB 8214201

⑦ Proprietor: BEECHAM GROUP PLC  
Beecham House Great West Road  
Brentford Middlesex TW8 9BD (GB)

⑥ Date of publication of application:  
23.11.83 Bulletin 83/47

⑦ Inventor: Elliott, Thomas Joseph  
13 Hervey Close  
Finchley London, N3 2HG (GB)  
Inventor: Murrell, Eispeth Anne  
49 Deepdene Vale  
Dorking Surrey (GB)

⑥ Publication of the grant of the patent:  
05.08.87 Bulletin 87/32

⑦ Representative: Dayneswood, Trevor et al  
Beecham Pharmaceuticals Patent and Trade  
Mark Department Biosciences Research Centre  
Great Burgh Yew Tree Bottom Road  
Epsom Surrey KT18 5XQ (GB)

⑧ Designated Contracting States:  
BE DE FR GB IT NL SE

⑨ References cited:  
GB-A- 901 659  
GB-A-1 239 965  
GB-A-1 489 133  
GB-A-2 028 319

The Merck Index, 10th Ed., 1983, p. 1191, 8135  
"Rosin Oil"

H. YANISTYN "Handbuch der Kosmetika und  
Riechstoffe", Vol. III, 1973, pp. 613-619

KIRK & OTHMER Encyclopedia of Chemical  
Technology, 3rd Ed., Vol. 24, pp. 154-155

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).

EP 0 094 771 B1

**Description**

This invention relates to topical compositions containing esters or ethers of Vitamin A (retinol) which are useful in the care of skin.

5 British Patent Specification No. 1,489,133 describes and claims a liquid, semi-liquid or gel composition comprising a topically acceptable oil-in-water or water-in-oil emulsion base and retinol acetate in an amount from 1,000 to 15,000 I Ug<sup>-1</sup>. Such compositions are of value in promoting epidermal mitosis and thus lead to a desirable thickening or plumping effect on the skin.

10 Published British Patent Application No. 2,026,319 describes and claims a similar composition to that of Specification No. 1,489,133, wherein the formulation of the emulsion base leads to high activity in skin thickening.

15 Although the compositions disclosed in the above two patent specifications give an enhanced skin thickening effect, the retinol acetate tends to decompose over a period of time, hence reducing the shelf life of the product. The decomposition is due largely to hydrolysis of the acetate by water in the emulsion base, followed by rapid oxidation of the free retinol. Furthermore, since retinol acetate is water insoluble it is normally mixed with a non-ionic surfactant, thereby forming a water soluble form, prior to incorporation into the emulsion base.

20 In has now been found that acceptable levels of skin thickening coupled with good stability can be obtained if a C<sub>1-10</sub>-alkyl ether or a C<sub>3-10</sub>-alkyl ester of retinol is used in place of retinol acetate. It has also been found that the C<sub>1-10</sub> ether or C<sub>3-10</sub> ester of retinol may be incorporated into an emulsion base either as a water soluble or water insoluble form.

Accordingly, the present invention provides a skin-care composition, comprising a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug<sup>-1</sup> of a C<sub>3-10</sub> alkyl ester or a C<sub>1-10</sub> alkyl ether of retinol.

25 Preferably, the composition of the invention comprises the all *trans*-isomer of a C<sub>1-10</sub> alkyl ether or a C<sub>3-10</sub> alkyl ester of retinol.

Preferably, the composition comprises a C<sub>1-7</sub>, straight chain, branched chain, or cyclo- alkyl ester of retinol; for example retinol propionate, butyrate, cyclopentanecarboxylate, pivalate, valerate, hexanoate, and heptanoate.

30 Preferred ethers of retinol for use in the composition of the invention are C<sub>1-7</sub> alkyl ethers, suitably the methyl ether of retinol is used.

Preferably, the composition comprises from 1,000 to 10,000 I Ug<sup>-1</sup>, or more suitably from 2,000 to 5,000 I Ug<sup>-1</sup> of a C<sub>1-10</sub> alkyl ether or a C<sub>3-10</sub> alkyl ester of retinol.

35 The preferred emulsion base is an oil-in-water emulsion base containing from 20 to 40% by weight of oil.

An emulsifier is preferably used in the composition of the invention, and this may be an anionic, cationic or non-ionic type. In order of their ability to produce a skin thickening effect, anionic emulsifiers are less effective than non-ionic emulsifiers which are in turn less effective than cationic emulsifiers. However, the latter can cause skin irritation when used, and non-ionic emulsifiers are, therefore, preferred.

40 It has been found that the proportion of non-ionic emulsifier in the compositions of the invention is not critical, but at least 1% by weight is preferred to give a stable emulsion. Suitably an amount in the range 2% to 12%, more suitably 4% to 8% is preferred.

Examples of oils suitable for inclusion in the present compositions include: volatile linear iso-paraffins, acyclic dimethylpoly siloxanes, cyclic dimethylpoly siloxanes, mineral oils, vegetable oils, synthetic fatty acid esters, fatty alcohols, lanolin and its derivatives.

45 Examples of non-ionic emulsifiers suitable for inclusion in the present compositions include: sorbitan monostearate, glyceryl monostearate, polysorbates, polyethylene derivatives of fatty alcohols.

The compositions of this invention should desirably include an anti-oxidant effective in preventing 50 oxidation of the retinol component and consequent reduction in the activity of the composition. Some anti-oxidants are effective in this respect but themselves oxidise to give a noticeable yellowing of the cream.

Two anti-oxidants which are particularly suitable for incorporation are butylated hydroxytoluene (BHT), (2,6-di-tert-butyl-p-cresol) and butylated hydroxyanisol (BHA), (2-tert-butyl-4-hydroxyanisole or 55 3-tert-butyl-4-hydroxyanisole) or a mixture of these. Accordingly in another of its aspects, the invention includes a composition in accordance with the invention including BHT and/or BHA as anti-oxidant.

The retinol component of the compositions may be dispersed in the emulsion in the form of a 'solubilised' mixture. Such mixtures are generally solutions of the retinol component in hydrophilic organic solvents such as glycerine and/or propylene glycol, together with a surfactant such as Tween® 80.

60 The skin-care compositions according to the invention, which comprise a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 I Ug<sup>-1</sup> of a C<sub>3-10</sub> alkyl ester or a C<sub>1-10</sub> alkyl ether of retinol, may be prepared by mixing the emulsion base with the retinol component.

65 Preferably, the retinol component is added to the emulsion base with stirring at a temperature of less than 50°C, suitably 35°C.

## 0 094 771

The C<sub>1-10</sub> alkyl ethers and C<sub>3-10</sub> alkyl esters of retinol are known compounds or can be prepared by procedures analogous to known preparative procedures.

The following are examples of compositions in accordance with the invention.

		Example 1	% w/w
5	Formulation		
	Sorbitan stearate		2.00
10	Polysorbate®60		2.00
	Cetyl alcohol		2.00
	Cetyl alcohol/PEG 40 Caster oil		2.50
15	Mineral oil		25.00
	Lanolin		2.50
20	Decyl oleate		2.00
	Preservatives		0.37
	Anti-oxidant (BHT)		0.20
25	Perfume		0.45
	Water soluble retinol propionate		3,000—7,000 IU/g
30	Deionised water to		100.00

Sorbitan stearate, polysorbate®60, cetyl alcohol, PEG 40 castor oil, mineral oil, lanolin, decyl oleate, anti-oxidant, and preservatives were blended together and heated to about 78°C. The mixture was added to water at 78°C with stirring. The mixture was homogenised then allowed to cool to 35°C.

Retinol propionate was added to the mixture with stirring. The mixture was again homogenised, then cooled to 25°C. Perfume was added with stirring.

The following Examples were prepared using a procedure analogous to that used in Example 1.

		Example 2	% w/w
40	Glycerol stearate/PEG 100 stearate		4.50
	Cetostearyl alcohol		4.50
45	Cetearyl octanoate		3.00
	Stearyl heptanoate		2.00
	Fatty acid ester of propylene glycol		4.00
50	Mineral oil/lanolin alcohol		3.00
	Octyl palmitate		5.00
	Mineral oil		5.00
55	Antioxidant (BHT)		0.20
	Propylene glycol		3.00
60	Preservatives		0.62
	Perfume		0.20
	Water soluble retinol cyclopentanoate		3,000—7,000 IU/g
65	Deionised water to		100.00

**0 094 771**

**Example 3**

		% w/w
5	Ceteareth®12	2.00
	Cetyl alcohol	8.00
	Squalane	10.00
10	Antioxidant (BHT)	0.20
	Propylene glycol	2.00
	Preservatives	0.37
15	Perfume	0.30
	Oil soluble retinol methyl ether	3,000—7,000 IU/g
20	Deionised water to	100.00

**Example 4**

		% w/w
25	Sorbitan stearate	1.50
	Polysorbate® 60	2.00
30	Glycerol stearate	4.00
	Cetyl alcohol	2.00
35	Octyl palmitate	3.00
	Mineral oil	8.00
	Decyl oleate	3.00
40	Anti-oxidant (BHT)	0.10
	Polyethylene microspheres	3.00
	Glycerine	5.00
45	Allantoin	0.10
	Propylene glycol	3.00
50	Preservatives	0.35
	Oil soluble retinol heptanoate	3,000—7,000 IU/g
	Perfume	0.20
55	Deionised water to	100.00

**Claims**

- 60     1. A skin-care composition, characterised in that it comprises a topically acceptable oil-in-water or water-in-oil emulsion base and from 1,000 to 15,000 IU<sup>-1</sup> of a C<sub>3-10</sub> alkyl ester or a C<sub>1-10</sub> alkyl ether of retinol.
2. A composition as claimed in claim 1, wherein the retinol component is the all *trans*-isomer.
3. A composition as claimed in claim 1 or 2, wherein the retinol component is a straight chain, branched chain, or cyclic C<sub>3-7</sub> alkyl ester of retinol.

## 0 094 771

4. A composition as claimed in claim 1 or 2, wherein the retinol component is a C<sub>1-7</sub> alkyl ether of retinol.
5. A composition as claimed in any one of claims 1 to 4, wherein the amount of the retinol component is from 1,000 to 10,000 I Ug<sup>-1</sup>.
- 5 6. A composition as claimed in claim 5, wherein the amount of the retinol component is from 2,000 to 5,000 I Ug<sup>-1</sup>.
7. A composition as claimed in any one of claims 1 to 6, wherein the emulsion base comprises from 20 to 40% by weight of oil.
8. A composition as claimed in any one of claims 1 to 7, including an emulsifying agent.
- 10 9. A composition as claimed in claim 8, wherein at least 1% by weight of the composition of a non-ionic emulsifying agent is present.
10. A composition as claimed in any one of claims 1 to 9, including an anti-oxidant.

### Patentansprüche

- 15 1. Eine Hautpflege-Zusammensetzung, dadurch gekennzeichnet, daß sie eine lokal verträgliche Öl-in-Wasser-oder Wasser-in-Öl-Emulsionsbasis und 1000 bis 15000 I Ug<sup>-1</sup> eines C<sub>3-10</sub>-Alkylesters oder eines C<sub>1-10</sub>-Alkyläthers von Retinol enthält.
2. Eine Zusammensetzung wie in Anspruch 1 beansprucht, in welcher die Retinol-Komponente in der 20 vollständigen Form vorliegt.
3. Eine Zusammensetzung wie in Anspruch 1 oder 2 beansprucht, in welcher die Retinol-Komponente ein geradkettiger, verzweigtkettiger oder cyclischer C<sub>3-7</sub>-Alkylester von Retinol ist.
4. Eine Zusammensetzung wie in Anspruch 1 oder 2 beansprucht, in welcher die Retinol-Komponente ein C<sub>1-7</sub>-Alkyläther von Retinol ist.
- 25 5. Eine Zusammensetzung wie in einem der Ansprüche 1 bis 4 beansprucht, in welcher die Menge der Retinol-Komponente von 1000 bis 10000 I Ug<sup>-1</sup> beträgt.
6. Eine Zusammensetzung wie in Anspruch 5 beansprucht, in welcher die Menge der Retinol-Komponente von 2000 bis 5000 I Ug<sup>-1</sup> beträgt.
7. Eine Zusammensetzung wie in einem der Ansprüche 1 bis 6 beansprucht, in welcher die 30 Emulsionsbasis 20 bis 40 Gewichtsprozent Öl enthält.
8. Eine Zusammensetzung wie in einem der Ansprüche 1 bis 7 beansprucht, welche ein Emulgiermittel enthält.
9. Eine Zusammensetzung wie in Anspruch 8 beansprucht, in welcher mindestens 1 Gewichtsprozent eines nicht-ionischen Emulgiermittels, bezogen auf die Zusammensetzung, vorliegt.
- 35 10. Eine Zusammensetzung wie in einem der Ansprüche 1 bis 9 beansprucht, welche ein Anti-Oxidationsmittel enthält.

### Revendications

- 40 1. Composition de soins pour la peau, caractérisée en ce qu'elle comprend une base d'émulsion du type huile-dans eau ou eau-dans-huile acceptable localement et de 1 000 à 15 000 IUG<sup>-1</sup> d'un ester alcoylique en C<sub>3-10</sub> ou d'un éther alcoylique en C<sub>1-10</sub> du rétinol.
2. Composition suivant la revendication 1, dans laquelle le composant rétinol est l'isomère tout trans.
3. Composition suivant la revendication 1 ou la revendication 2, dans laquelle le composant rétinol est 45 un ester alcoylique en C<sub>3-7</sub>, à chaîne droite, ramifiée ou cyclique du rétinol.
4. Composition suivant la revendication 1 ou la revendication 2, dans laquelle le composant rétinol est un éther alcoylique en C<sub>1-7</sub> du rétinol.
5. Composition suivant l'une quelconque des revendications 1 à 4, dans laquelle la quantité du composant rétinol est de 1 000 à 10 000 IUG<sup>-1</sup>.
- 50 6. Composition suivant la revendication 5, dans laquelle la quantité du composant rétinol est de 2 000 à 5 000 IUG<sup>-1</sup>.
7. Composition suivant l'une quelconque des revendications 1 à 6, dans laquelle la base d'émulsion comprend de 20 à 40 % en poids d'huile.
8. Composition suivant l'une quelconque des revendications 1 à 7, comprenant un agent émulsifiant.
- 55 9. Composition suivant la revendication 8, dans laquelle il y a au moins 1 % en poids d'un agent émulsifiant non-ionique.
10. Composition suivant l'une quelconque des revendications 1 à 9, comprenant un anti-oxydant.